The Final Phase: Bringing Momelotinib to Patients

A Data Update and KOL Discussion
June 21, 2021
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Today’s Agenda

- Welcome & Introduction
- Momelotinib’s Impact on the Burdens of Myelofibrosis
- Importance of Treating Anemia in Myelofibrosis
- Association Between Transfusion Independence and Overall Survival; Impact on Transfusion Independence by Baseline Status
- Panel Discussion

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Importance of Treating Anemia in Myelofibrosis

Stephen Oh, MD, PhD
Siteman Cancer Center
Washington University School of Medicine
Momelotinib Progress Update

Stephen Dilly, MBBS, PhD
President & Chief Executive Officer
MOMENTUM Enrollment Complete!

195 Patients Enrolled vs. 180 Planned
Momelotinib Progresses as Sierra’s Flagship Compound

**MOMENTUM Progress**
- Trial has completed enrollment with 195 patients
- Topline data anticipated Q1 2022
- Completes data set for FDA filing

**Myelofibrosis Opportunity**
- MMB profile offers unique value proposition for underserved MF patients
- Potential for MMB combination studies

**Near-term Focus with Long-term Planning**
- Preparing for NDA filing and potential US launch
- Identifying early-stage programs with significant promise

On a Quest to Deliver Targeted Therapies for Rare Cancers
Pivotal Phase 3 ‘MOMENTUM’ Study: Enrollment Complete and Awaiting Topline Results

*Danazol was selected as an appropriate comparator given its use to ameliorate anemia in MF patients, as recommended by NCCN, ESMO guidelines.

**Primary Endpoint**
- Total symptom score (TSS) response rate at Week 24

**Secondary Endpoints**
- Transfusion independence (TI) rate at Week 24
- Splenic response rate (SRR) at Week 24
Significant Need Remains in Myelofibrosis Treatment

Improved Survival
- Generally incurable (for most)
- Median survival is 2-8 years after diagnosis driven by degree of anemia, other factors
- Durability of activity
  - Current treatments are often dose limited by platelet counts, anemia
  - Favorable hematologic safety profile could enable long term higher dose intensity and durable disease control

Therapy for Cytopenic Patients
- Anemia
  - Common and progressive
  - Current treatments worsen anemia
- Thrombocytopenia
  - Can be a manifestation of disease
  - Current treatments decrease platelet levels

Anemia is a major problem. …It's present at…[diagnosis]… in about a third of patients. …after 1 year, two-thirds are already anemic. I don’t have a good medication to give them. Patients may have exacerbation of anemia while on JAK inhibitors. Anemia is a target for new medication to develop
– Srdan Verstovsek, MD, PhD

Our goals for the future are to expand the breadth of response, beyond spleen and symptoms, … to include progression-free and overall survival…and to improve anemias or cytopenias
– Ruben Mesa, MD

One area that needs significant attention is patients who have myelofibrosis and thrombocytopenia. …in addition to having worse overall survival, these patients do not have good treatment options
– Pankit Vacchini, MD

(2) Source: Edited transcript from Ongoing Unmet Needs and New Approaches in Myelofibrosis, OncLive, April 14, 2021.
Current Treatment Paradigm Comes at a Cost

Current Treatment Goal: Managing Spleen and/or Symptoms

- Enlarged Spleen: 50 – 70% of patients at diagnosis
- Symptoms: 40 – 60% of patients at diagnosis

Comes at a Cost: Worsening Anemia and/or Thrombocytopenia

- Anemia / Transfusions: 70 – 90% of patients at diagnosis
- Low Platelet Count: 10 – 30% of patients at diagnosis

Additional Factors Should be Considered in Future Treatment Paradigm

Source: Internal data on file.
All Four Factors Play a Role in Treatment Decisions

Optimal Treatment Goal: Durably Manage Spleen, Symptoms & Anemia / Transfusion Requirements while Maintaining Platelet Count and Dose Intensity

- **Enlarged Spleen**: 50 – 70% of patients at diagnosis
- **Symptoms**: 40 – 60% of patients at diagnosis
- **Anemia / Transfusions**: 70 – 90% of patients at diagnosis
- **Low Platelet Count**: 10 – 30% of patients at diagnosis

Hemoglobin Level and Platelet Count Must be Considered When Choosing Future Treatment

Source: Internal data on file.
Mechanism of Action: Momelotinib Inhibits JAK1, JAK2 and ACVR1/ALK2

Hyperactive JAK-STAT signaling results in overproduction of multiple inflammatory cytokines in MF, which act both locally and systemically.

Preclinical and clinical studies suggest that the clinical anemia benefits of momelotinib result from suppression of ACVR1/ALK2-mediated hepcidin production.

Momelotinib Inhibits all Three Disease Drivers, Potentially Improving Splenomegaly and Symptoms of Myelofibrosis While Maintaining or Improving Hemoglobin

Momelotinib’s Unique MOA May Lead to Durable Responses for Symptomatic & Anemic MF Patients

MMB has the Potential to Provide Significant and Durable Benefits for Patients with MF

- Clinically meaningful anemia benefits, symptom and spleen control, without impacting platelets
- Low potential for myelosuppression supports dosing intensity & durable activity
- Some patients remain on full dose of MMB for >10 years
- Robust and meaningful survival duration achieved in both the JAKi-naïve and JAKi-exposed patients

MMB is a Differentiated JAK Inhibitor Enabling Clear Patient Segmentation

- Reduced transfusion burden and improved transfusion independence for anemic patients and those at risk of developing anemia
  - Achieving TI could become the primary driver of treatment decisions in MF
- MMB retains robust activity irrespective of baseline platelet count
- Optimal treatment for patients with MF who are, or are at risk of becoming, anemic and/or thrombocytopenic
Completed Phase 3 Studies SIMPLIFY-1 and 2

**SIMPLIFY-1**

**1st-Line Population**  
JAK inhibitor naïve

<table>
<thead>
<tr>
<th>Goal</th>
<th>Non-Inferiority</th>
<th>Superiority</th>
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<tbody>
<tr>
<td>Endpoints at Week 24:</td>
<td></td>
<td></td>
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<tr>
<td>SRR ≥35% (primary)*</td>
<td>27%</td>
<td>7%</td>
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<tr>
<td>Symptom score reduction ≥50%</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>TI for ≥12weeks</td>
<td>67%</td>
<td>43%</td>
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*Met endpoint  
**Journal of Clinical Oncology**, 2017 35(34):3844

**SIMPLIFY-2**

**2nd-Line Population**  
Prior ruxolitinib complicated by hematologic toxicity

<table>
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<tr>
<th>Goal</th>
<th>Non-Inferiority</th>
<th>Superiority</th>
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<tbody>
<tr>
<td>Endpoints at Week 24:</td>
<td></td>
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<tr>
<td>SRR ≥35% (primary)</td>
<td>88.5% RUX/RUX+</td>
<td>7%</td>
</tr>
<tr>
<td>Symptom score reduction ≥50%</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>TI for ≥12weeks</td>
<td>67%</td>
<td>43%</td>
</tr>
</tbody>
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*Met endpoint  
**Journal of Clinical Oncology**, 2017 35(34):3844
SIMPLIFY-1 Trial: Safety Results

Safety Generally Similar for Momelotinib, Ruxolitinib in the 24-week Double-blind Period

- Grade 3 or 4 hematological AEs were very low for momelotinib
- Anemia and thrombocytopenia were more common in the ruxolitinib arm
- Nausea was more common with momelotinib
- No evidence of long-term toxicity observed during extended momelotinib dosing up to 10 years

SIMPLIFY-1

| 24-Week RT Period | MMB  
(N=214) | RUX  
(N=216) |
<table>
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<tbody>
<tr>
<td>Select TEAEs, by PT</td>
<td></td>
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<tr>
<td>Grade 3/4 TEAEs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with any Gr3/4 TEAE, n (%)</td>
<td>74 (34.6%)</td>
<td>94 (43.5%)</td>
</tr>
<tr>
<td>Gr3/4 Thrombocytopenia</td>
<td>15 (7.0%)</td>
<td>10 (4.6%)</td>
</tr>
<tr>
<td>Gr3/4 Anemia</td>
<td>13 (6.1%)</td>
<td>49 (22.7%)</td>
</tr>
<tr>
<td>Gr3/4 Pneumonia</td>
<td>5 (2.3%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Any Grade TEAEs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with Any Grade TEAE, n (%)</td>
<td>198 (92.5%)</td>
<td>206 (95.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39 (18.2%)</td>
<td>43 (19.9%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>31 (14.5%)</td>
<td>81 (37.5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>40 (18.7%)</td>
<td>63 (29.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (15.9%)</td>
<td>8 (3.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (14.5%)</td>
<td>26 (12.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>38 (17.8%)</td>
<td>43 (19.9%)</td>
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1 RT = Randomized Treatment
Importance of Treating Anemia in Myelofibrosis

Stephen Oh, MD, PhD
Siteman Cancer Center
Washington University School of Medicine
Anemia is a Significant Burden for Myelofibrosis Patients

Anemia is present in 70%-90% of MF patients at diagnosis
• ≥13g/dl is considered normal (1)

Progressive anemia and transfusion requirements are common

Aberrant activation of hepcidin transcription via hyperactivated ACVR1 signaling resulting in profound functional iron deficiency anemia

Impact on patient quality of life and survival (2)
• Fatigue is the number 1 complaint – unable to carry out day-to-day activities
• Transfusion burden
  – About 60% of patients will receive at least one blood transfusion
    o Transfusion reactions and infection can occur
  – Physicians categorize 15-20% of MF patients as transfusion-dependent
    o Have to monitor for iron overload, build up of autoantibodies

Anemia response correlates with improved quality of life in myelofibrosis patients with anemia (3)

(2) Internal data on file
Anemia and Hepcidin Predict Poor Survival in Myelofibrosis

**Anemia of inflammation** driven by elevated hepcidin

**Elevated hepcidin** inhibits iron transport and iron homeostasis

Anemia and elevated hepcidin are **negative prognostic indicators**

New therapies should provide anemia benefits in addition to symptom, spleen benefits

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**Anemia predicts poor survival in myelofibrosis**

- **No anemia** (Hb ≥12 g/dL)
  - Median survival: 7.9 years
- **Mild anemia** (Hb 10-12 g/dL)
  - Median survival: 4.9 years
- **Moderate anemia** (Hb 8-10 g/dL)
  - Median survival: 3.4 years
- **Severe anemia** (Hb <8 g/dL)
  - Median survival: 2.1 years

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**Hepcidin predicts poor survival in myelofibrosis**

- **Low hepcidin**
- **High hepcidin**

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Nicosi M et al, Leukemia 2018

Pardanani et al, American Journal of Hematology 2013
Momelotinib Treatment Appears to Lead to Increased Transfusion Independence

SIMPLIFY-1

A higher rate of Transfusion Independence was achieved at week 24 with MMB when compared to RUX in S1

In S1, the transfusion burden for MMB treatment was ~half that of RUX patients (HR 0.52; p < 0.001)

Overall Survival in JAKi-naïve and JAKi-exposed Patients

**SIMPLIFY-1**

**JAKi-naïve Patients**

- **Week 24 Crossover to open-label MMB**
- **Median OS 53.1 months in RUX→MBB patients**
- **Median not reached in originally MMB-randomized patients**

**SIMPLIFY-2**

**JAKi-exposed Patients**

- **Week 24 Crossover to open-label MMB**
- **Median OS 37.5 months for BAT/RUX→MBB patients**
- **Median OS 34.3 months for originally MMB-randomized patients**

Durable survival reflects momelotinib benefit on extended treatment or crossover to momelotinib, regardless of starting therapy.

The OS results are amongst the best survival reported in patients who have been previously treated with ruxolitinib.

Transfusion Independence Associated with Improved Overall Survival in Myelofibrosis Patients Receiving MMB

and Transfusion Independence Seen Irrespective of Baseline Degree of Anemia, Platelet Count or Transfusion Status

Aaron Gerds, MD
Taussig Cancer Institute,
Cleveland Clinic
Methods for Evaluating the Association Between Transfusion Independence and Overall Survival

- The relationship between W24 response endpoints and overall survival (OS) was explored in patients randomized to MMB in S1 and S2
  - Response endpoints include W24 Transfusion Independence, Spleen and Symptom (TSS) response
  - Survival from baseline was estimated using K-M analysis with descriptive log-rank tests for comparison applied (all p values are descriptive)
  - Hazard ratios were computed using proportional hazard regression
  - To adjust for the time to response bias, OS from W24 was also compared

- As patients randomized to the control arm in both studies crossed over to open label MMB after 24 weeks of randomized treatment, a valid comparison of OS with patients randomized to RUX or BAT/RUX vs MMB was not possible, therefore, only the MMB arm was analyzed

- W24 Transfusion Independence rates were also explored for MMB and RUX randomized patients in S1 for subsets by baseline hemoglobin, platelet counts and transfusion status

Transfusion Independence with Momelotinib is Associated with Improved Overall Survival, Including Anemic Patients

Mesa, R. et.al. European Hematology Association, June 2021, oral presentation S202; Virtual.

Achieving or Maintaining TI Predicted Better Survival in Patients Treated with Momelotinib. The Goal of Achieving TI Should Become an Important Driver of Treatment Decisions.

Week 24 TI response = no RBC transfusion for ≥ 12 weeks immediately prior to Week 24, Hgb level ≥ 8 g/dL
Transfusion Independence is Achieved Irrespective of Baseline Degree of Anemia, Platelet Count or Transfusion Status

The W24 TI-R rate in S1 was higher in patients randomized to MMB vs RUX, irrespective of the degree of baseline anemia, or the baseline PLT count or transfusion status

Week 24 Transfusion Independence Response (TI-R): no RBC transfusion within ≥ 12 weeks immediately prior to Week 24, with Hgb ≥ 8 g/dL

Transfusion Dependent (TD): ≥4 units of RBCs or Hgb level, ≤ 8 g/dL in the 8 weeks prior to randomization

Transfusion Independent (TI): absence of RBC transfusions and no Hgb < 8 g/dL in the 12 weeks prior to randomization

Transfusion Requiring (TR): neither TD nor TI

Conclusions & Clinical Relevance

• MMB demonstrated robust overall survival in both JAKi-naïve and JAKi-exposed patients
  
• W24 TI Response predicted better survival in patients treated with MMB
  
• W24 TI Response rate was higher in patients randomized to MMB vs RUX, irrespective of the degree of baseline anemia, or the baseline platelet count or transfusion status
  
• Taken together, these data further support the potential benefit of MMB's ACVR1/ALK2 inhibitor activity in addition to inhibiting JAK1 and JAK2, may lead to improved TI rates and overall survival
  
• Achieving TI could become the primary driver of treatment decisions in MF
  
• As a result, MMB has the potential to become a preferred treatment for patients with MF who are anemic or who are at risk of myelosuppression as a result of treatment with currently available JAK inhibitors
Panel Discussion and Q&A

Key Opinion Leaders:
- Aaron Gerds, MD
- Stephen Oh, MD, PhD
- Srdan Verstovsek, MD, PhD

Sierra Management:
- Barbara Klencke, MD
- Stephen Dilly, MBBS, PhD
Aaron Gerds, MD, completed his undergraduate degree, a BA in biology and chemistry, with honors at Hope College in Holland, Michigan and obtained his MD from Loyola University Chicago Stritch School of Medicine. He continued his Internal Medicine residency at Loyola University Hospital where he served as chief resident. In Chicago, he became interested in hematology clinical trials which led him to pursue a master’s degree in clinical research methods and epidemiology. Dr. Gerds completed his hematology and oncology fellowship at the University of Washington, Fred Hutchinson Cancer Research Center, in Seattle and pursued a subspecialty in treating patients with myeloproliferative neoplasms (MPNs) such as polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF), as well as other myeloid disorders. During his fellowship, he was awarded the ASBMT’s New Investigator Award.

Dr. Gerds is an Associate Professor of Medicine and the Deputy Director for Clinical Research at the Cleveland Clinic Taussig Cancer Institute where he serves as the principal investigator for several clinical trials for the treatment of MPNs and myeloid neoplasia with a focus on developing new treatments for these patients. He is also an active member of the American Society of Hematology, participating in both the Advocacy Leadership Institute and Clinical Research Training Institute, as well as serving as Chair of the Committee on Communications, as a member of the Test Materials Development Committee, former Editor of the ASH News Daily, and current Editor-in-Chief of ASH Clinical News. Dr. Gerds serves as the Medical Director for the Case Comprehensive Cancer Center’s Clinical Research Office and is co-PI for the Center’s LAPS grant. He is also the institutional PI for the SWOG Cancer Research Network and is part of the leadership on several national clinical trials and is the chair of the National Comprehensive Cancer Network (NCCN) Myeloproliferative Neoplasms and Systemic Mastocytosis Guidelines.
Stephen Oh, MD, PhD

Dr. Stephen Oh is an Associate Professor, Department of Medicine, (Hematology Division) and Pathology and Immunology at the Washington University School of Medicine.

Dr. Oh received his M.D. and Ph.D. in Cancer Biology from the Northwestern University Feinberg School of Medicine. He completed his Internal Medicine Residency, Hematology/Oncology Fellowship, and Postdoctoral Fellowship at Stanford University.
Srdan Verstovsek, MD, PhD

Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Dr Srdan Verstovsek is a medical oncologist and professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center, Houston, Texas. He obtained his medical and doctoral degree at the University of Zagreb, Zagreb, Croatia. Dr Verstovsek’s clinical and translational research is focused on understanding the biology of and developing new therapies for myeloproliferative neoplasms (MPNs). He is Director of the Clinical Research Center for MPNs at MD Anderson. He has been principal investigator for more than 50 clinical trials testing novel therapies for patients with MPNs and has published more than 400 peer-reviewed manuscripts. Dr Verstovsek is actively involved with national patient groups and is a frequently invited speaker on MPNs both nationally and internationally. In 2010, he was awarded the Celgene 2010 Young Investigator Award for Clinical Research in Hematology, and in 2011, he was awarded the Distinguished Alumnus Award, Division of Cancer Medicine, MD Anderson. In 2013, Dr Verstovsek was awarded the 7th Annual Irwin H. Krakoff Award for Excellence in Clinical Research by the Division of Cancer Medicine, MD Anderson, and the Distinguished Lecturer Award from the Society of Hematologic Oncology. In 2015, Dr Verstovsek was elected as a member of The American Society for Clinical Investigation in recognition of his contributions as a physician-scientist. In 2017, Dr Verstovsek was awarded the Otis W. and Pearl L. Walters Faculty Achievement Award in Clinical Research by MD Anderson Cancer Center.